B27

COVID 19 (nCorona) Virus Outbreak Control and Prevention State Cell

Health & Family Welfare Department

Government of Kerala

COVID-19 INTERIM TREATMENT GUIDELINES FOR KERALA STATE

No./31/2020/Health – 24th March 2020

WHO has declared the COVID-19 epidemic affecting more than 195 countries as a Pandemic. Due to the inflow of persons from affected countries, Kerala state has strengthened the surveillance and control measures against the disease.

This document was developed as a clinical guideline to streamline the treatment efforts against SARS-CoV -2 virus. It is a 'living' document and will be updated from time to time depending on newer discovery and current research.

1. Laboratory investigation for proven COVID 19 patients

At Admission	CBC, RFT, LFT, CRP, RBS, ECG
If clinically Indicated	Portable CXR, HIV, HBsAg, HCV, D-Dimer, Ferritin, LDH, CPK, procalcitonin, Blood culture
To repeat Every 3 days if clinically deteriorating.	CBC, Creatinine, AST/ALT, CRP, LDH, CPK, Ferritin, HRCT
For Immunocompromised patients eg Transplant recipients, HIV	Tests to rule out opportunistic infections like Mycobacterium tuberculosis, pneumocystis jiroveci etc

2. Categories

A	Mild sore throat / cough / rhinitis /diarrhea
B	Fever and/or severe sore throat / cough /diarrhea OR Category-A plus two or more of the following • Lung/ heart / liver/ kidney / neurological disease/ Hypertension / haematological disorders/ uncontrolled diabetes/ cancer /HIV-AIDS • On long term steroids /immunosuppressive drugs. • Pregnant lady • Age –more than 60 years. OR Category A Plus cardiovascular disease
C	• Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs] • Children with ILI (influenza like illness) with ***red flag signs*** (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnoea /respiratory distress, etc). • Worsening of underlying chronic conditions.

*Categorization should be reassessed every 24-48 hours for Category A & B

3. Identification of high risk patients

Co morbidities	Clinical assessment	Laboratory values
Uncontrolled diabetes	Hypoxia – SpO2 ≤ 93% on room air	CRP > 100 mg /L
Hypertension	Tachycardia PR > 125/min	CPK > twice upper limit of normal
Cardiovascular disease	Respiratory distress RR > 30/min	
Lung disease	Hypotension BP < 90systolic, 60mm Hg Diastolic.	Ferritin > 300mcg/L
CKD	Altered sensorium	TROP T elevation
CLD		LDH > 245 U /L
On immunosuppressives		D Dimer > 1000ng/ml
HIV / congenital immunodeficiency disorders		Multi organ dysfunction
Age > 60yrs		ALC < 0.8

4. Treatment

1. Categorize A, B , C
2. Treatment

Supportive care

1. AVOID using NSAIDs other than paracetamol unless absolutely necessary.
2. AVOID using nebulized drugs to avoid aerosolization of virus, use MDI instead.
3. Oseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR report with dose adjustment for paediatric and renal insufficiency
4. Antibiotic selection in case of secondary bacterial pneumonia should be as per institutional antibiogram.
5. AVOID using systemic steroids. Steroids may be considered only in case of refractory shock, macrophage activation syndrome or in Cytokine release syndrome (CRS) Grade 3 or 4 with no response to Tocilizumab.
6. Non-invasive ventilation [NIV] is to be avoided in patients with COVID-19, as there is high risk of aerosol generation as the seal they generate is inferior to that cheived with a correctly placed and inflated cuffed tracheal tube.
7. Consider discontinuation of inhaled steroids as they may reduce local immunity and promote viral replication. But if discontinuation of inhaled steroids is likely to worsen the preexisting lung disease, decision on the same has to be taken by the treating doctor.

Treatment strategies according to clinical situation

Category	Treatment	Precautions
A	Symptomatic treatment	Categorization should be reassessed every 28-48 hours for Category A.
B	1. Tab HCQs 400mg 1-0-1 x 1 day, then 200 1-0-1 x 4 days (Children : 6.5mg/kg/ dose PO BD day 1 followed by 3.25mg/kg/dose PO BD X 4 days) OR Tab Chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h	Contraindications to chloroquine /HCQS • QTc > 500msec • Porphyria • Myasthenia gravis • Retinal pathology • Epilepsy Pregnancy is NOT a contraindication

	later, followed by 300 mg (5 mg/kg) BD up to Day 5 Plus 2. Tab Azithromycin 500mg 1-0-0 x 1 day and 250mg 1-0-0 x 4 days Children: 10 mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5. 3. Tab Oseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR report. Children : 3mg/kg/dose BD Dose adjustment for those with renal insufficiency	If Baseline QT is prolonged – frequent ECG monitoring is required
C	1. Tab HCQs 400mg 1-0-1 x 1 day, then 200mg 1-0-1 x 4 days Children : 6.5mg/kg/ dose PO BD day 1 followed by 3.25mg/kg/dose PO BD X 4 days OR Tab Chloroquine base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5. [Usually 1tablet of chloroquinė has 150 mg base] PLUS Inj Azithromycin 500mg IV stat and 250mg IV OD for 5 days Children: 10mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5. 2. Tab Lopinavir / Ritonavir (400/100) 1-0-1 for 14 days	For chloroquine and derivatives as discussed above For Protease inhibitors Assess for drug-drug interactions (including with calcineurin inhibitors) before starting. Gastrointestinal intolerance may be seen Monitor liver function tests while on therapy. Discontinue these agents upon discharge regardless of duration, unless previously used as maintenance medications for another indication.

	or for 7 days after becoming asymptomatic. Children 14 days to 6 months : 16mg/kg (based on lopinavir component) PO BD < 15kg : 12 mg/kg PO (based on lopinavir component BD) 15-25 kg: 200 mg-50 mg PO BD 26-35 kg: 300 mg-75 mg PO BD >35 kg: 400 mg-100 mg PO BD Lopinavir/ritonavir is to be used only if HCQS/chloroquine is contraindicated. Lopinavir/ritonavir should be used only on a compassionate ground after informed consent. It has to be started within 10 days of symptom onset. 3. Tab Oseltamivir 75mg 1-0-1 in all symptomatic patients with influenza like illness until PCR report with dose adjustment for children and those with renal insufficiency	
If CAT C patient progresses to ARDS/ MODS while on HCQS/chloroquine plus azithromycin, addition of Lopinavir/ritonavir may be considered in case of progressive worsening as Remedesivir is not available in India. In that case azithromycin is to be stopped. QTc is to be monitored very frequently. This combination is to be used on a compassionate ground after taking informed consent explaining the possibility of life threatening QTc prolongation and cardiac arrhythmias.		

For those with evidence of cytokine release syndrome [CRS]

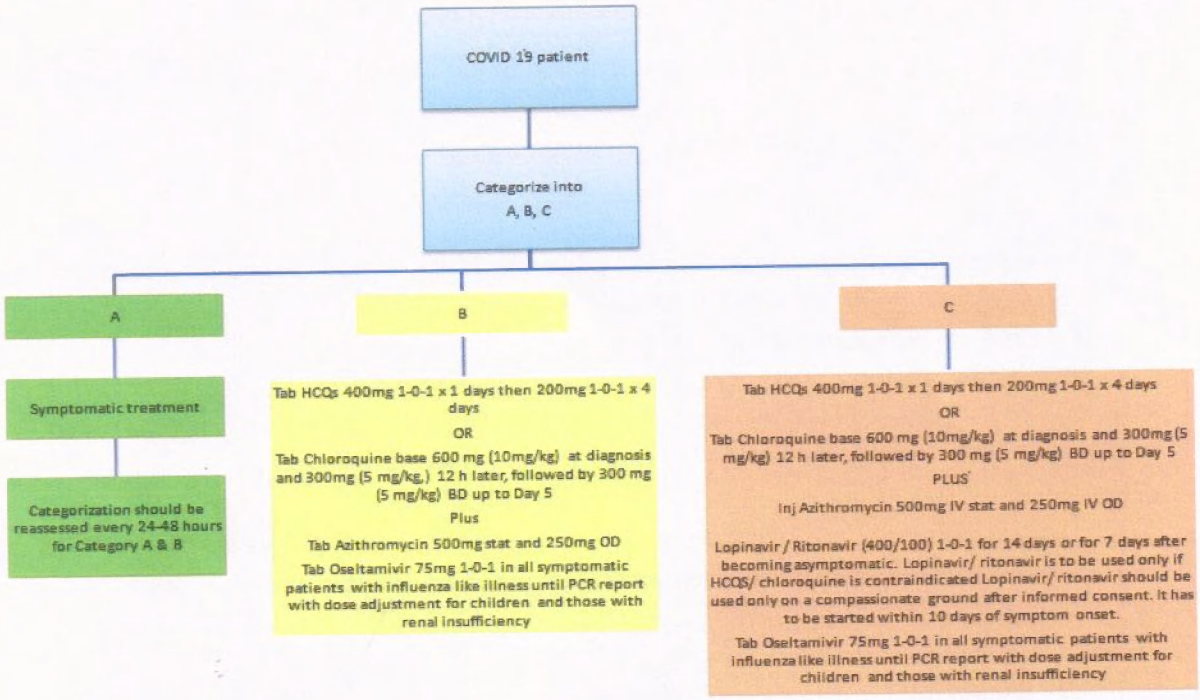
Grade	Clinical Assessment	Treatment
Grade 1	Mild reaction: low grade fever, No oxygen requirement or need for IVF	No treatment

Grade 2	Moderate reaction : -High grade fever (> 103F), need for IVF (not hypotension), mild oxygen requirement (<6L/min) -Grade 2 AKI -Grade 3 LFT (Raised liver enzymes and S. Bilirubin ≥ 2.5gm/dl)	Send for serum IL-6, If not available , use CRP as a surrogate marker
Grade 3	Severe reaction : -Rapidly worsening respiratory status with radiographic infiltrates and spo2 ≤ 93% in room air or on supplemental oxygen (> 6L/min, high flow, BiPAP, CPAP) - Grade 4 Liver function test (raised liver enzymes, S Bilirubin > 2.5gm/dl and INR > 1.5, encephalopathy) -Grade 3 AKI; -IVF for resuscitation , - coagulopathy requiring correction with FFP or cryoprecipitate -low dose vasopressor (Noradrenaline < 0.5mcg/kg/min or Adrenaline < 0.3mcg/kg/min)	Send for serum IL-6 or CRP, Ferritin Consider tocilizumab >18 years : 8mg/kg IV (max 400mg) < 18 years < 30kg : 12mg/kg IV over 60 minutes >30kg : 8mg/kg (max 800mg) IV over 60minutes if no effect can repeat x 2 more doses Q8H apart; if no response, consider low dose corticosteroids especially in case of concomitant septic shock
Grade 4	Life threatening multi organ dysfunction, hypoxia requiring mechanical ventilation, hypotension requiring high dose vasopressors	Send for serum IL-6 or CRP; consider tocilizumab as in Grade 3; consider corticosteroids

(Adapted and modified from the Penn CRS criteria and MGH)

For Grade 3/ 4 CRS when there is no response to Tocilizumab / availability/tolerance issue

Glucocorticoids may be used for a short period of time – 3-5 days. It is recommended that dose should not exceed the equivalent of methylprednisolone 1-2mg/kg/day. A larger dose of glucocorticoid will delay the removal of corona virus due to immunosuppressive effects.



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C	Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs] Children with ILI (influenza like illness) with ***red flag signs*** (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnoea /respiratory distress, etc). Worsening of underlying chronic conditions.

Contraindications to chloroquine /HCQS

- QTc > 500msec
- Porphyria
- Myasthenia gravis
- Retinal pathology
- Epilepsy

Pregnancy is NOT a contraindication
If Baseline QT prolongation – Monitor ECG

For Protease inhibitors
Assess for drug-drug interactions (including with calcineurin inhibitors) before starting.
Gastrointestinal intolerance may be seen
Monitor liver function tests while on therapy.
Discontinue these agents upon discharge regardless of duration, unless previously used as maintenance medications for another indication

If CAT C progresses to ARDS/MODS on HCQ/Chloroquine plus Azithromycin, addition of lopinavir / ritonavir may be considered

In Children: HCQs 6.5mg/kg/ dose BD, day 1 followed by 3.25mg/kg/dose PO BD X 4 days
Azithromycin: 10mg/kg (max 500mg) day 1, Followed by 5mg/kg/day on days 2 to 5.
Lopinavir/Ritonavir (based on lopinavir component): 14 days to 6months : 16mg/kg PO BD, < 15kg : 12 mg/kg PO, 15-25 kg: 200 mg-50 mg PO BD, 26-35 kg: 300 mg-75 mg PO BD, >35 kg: 400 mg-100 mg PO BD

The National Task force for COVID-19 constituted by ICMR recommends the use of hydroxy-chloroquine for prophylaxis of SARS-CoV -2 infection for high risk population.

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19.
2. Asymptomatic household contacts of laboratory confirmed cases
3.

DOSE

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks : to be taken with meals.
2. Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice day on Day 1, followed by 400 mg once weekly for next 3 weeks, to be taken with meals.
3.

Exclusion/contraindication

1. Drug is not recommended for prophylaxis in children under 15 years of age.
2. Drug is contraindicated in persons with retinopathy, hypersensitivity to HCQS or 4-aminoquinoline compounds

References

1. Massachusetts General Hospital COVID-19 Treatment Guidance
2. Interim Clinical Guidance For Patients Suspected Of/Confirmed with COVID – 19 in Belgium 19 March 2020
3. COVID 19 Management protocol, All India Institute of medical sciences, New Delhi
4. Novel Corona Virus Pneumonia diagnosis and treatment scheme for severe and critical cases – COVID 19 Medical care team Central Directive Group of China 13 March 2020
5. Diagnosis and treatment protocol for Novel Corona Virus Pneumonia trial version 7, National health commission China March 3, 2020

Available evidence on the use of Tocilizumab in COVID-19

Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor

Rationale for use of Tocilizumab in COVID-19

Pro-inflammatory cytokine levels are elevated in COVID-19 infection. Predictors of mortality from a retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China included elevated ferritin and IL-6. This suggests that virus induced hyper inflammation is contributing to the mortality[1, 2].

Tocilizumab has been found useful in severe or life threatening cases of cytokine release syndrome (CRS) due to chimeric antigen receptor-T cell therapy. However there are no randomized control trials that compared Tocilizumab versus steroids fir CRS [3].

Dose recommended for CRS:
>18 years: 8mg/kg IV (400mg),
< 18 years
< 30kg: 12mg/kg IV over 60 minutes
>30kg: 8mg/kg (max 800mg) IV over 60minutes
The total tocilizumab dose should not exceed 800 mg[4].
If no effect can repeat x 2 more doses Q8H apart;
If no response, consider low dose corticosteroids especially in case of concomitant septic shock
Can be given as an intravenous infusion in normal saline over 1 hour.
Up to 3 additional doses can be administered with at least 8 hour interval between consecutive doses.

Evidence for Tocilizumab in COVID-19
Xu et al reported their experience with Tocilizumab in patients with severe or critical COVID-19 infection[5]. The diagnosis of severity was defined if any of the following conditions was met: (1) respiratory rate $\geq$ 30 breaths/min; (2) SpO2 $\leq$ 93% while breathing room air; (3) PaO2/FiO2 $\leq$ 300 mmHg. A critical case was diagnosed if any of: (1) respiratory failure which requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, need to be admitted to ICU. The study included 21 patients who received standard therapy including lopinavir, methylprednisolone, other symptom relievers and oxygen therapy along with tocilizumab. The dose of Tocilizumab used was 400mg single intravenous infusion. 19 patients were discharged from hospital, while two were improving in hospital at the time of reporting. The authors also reported that symptoms, hypoxygenemia, and CT opacity changes were improved immediately after the treatment with tocilizumab in most of the patients.

Ongoing clinical trials:
Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (TOCIVID-19)
This is a multicenter, single-arm, open-label, phase 2 study in severe COVID-19 infection. All the patients enrolled are treated with tocilizumab. One-month mortality rate is the primary end point. Participants will receive two doses of Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours. Primary outcome measurement: 1 month mortality.

Guidelines and recommendations:
1) Recommendations for COVID-19 clinical management, National Institute for the Infectious Diseases, Italy:
Tocilizumab: 8 mg/kg (maximum 800 mg/dose), single dose intravenously (1-hour infusion); in absence or with poor clinical improvement a second dose should be administered after 8-12 hours.
Tocilizumab administration should be guided by the presence of 1 or more of following selection criteria: a) PaO2/Fi02 ratio < 300, b)rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation c)IL-6 levels >40 pg/ml (if not available, see D-dimer levels >1000 ng/ml.)

Therapeutic schedule: 2 administrations (each 8 mg/kg, maximum 800 mg). Second administration to be started at 8-12 hours from the first one. Repeat PCR and D-dimer (+/-IL-6) after 24 hours from each administration.

2) Massachusetts General Hospital COVID-19 Treatment Guidance:

To be given after establishment of clinical status

Grade 1 – mild reaction
Grade 2 – moderate reaction, fever, need for IVF (not hypotension), mild oxygen requirement
Grade 3 – severe, liver test dysfunction, kidney injury, IVF for resuscitation, low dose vasopressor, supplemental oxygen (high flow, BiPAP, CPAP)
Grade 4 – life threatening, mechanical ventilation, high dose vasopressors

Treatment interventions based on grades:

Grade 1 – no treatment
Grade 2 – send for serum IL-6
Grade 3 – send for serum IL-6; consider Tocilizumab, if no effect can repeat x 2 more doses Q8H apart; if no response, consider low dose corticosteroids
Grade 4 – send for serum IL-6; consider Tocilizumab as Grade 3; consider corticosteroids

References:

1. COVID-19: consider cytokine storm syndromes and immunosuppression - The Lancet [Internet]. [cited 2020 Mar 21]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext
2. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. - PubMed - NCBI [Internet]. [cited 2020 Mar 21]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32125452
3. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. - PubMed - NCBI [Internet]. [cited 2020 Mar 21]. Available from: https://www.ncbi.nlm.nih.gov/pubmed?term=27913530
4. ACTEMRA (tocilizumab) injection. Drug monograph
5. Xu et al Effective Treatment of Severe COVID-19 Patients with Tocilizumab. China Xiv:202003.00026v1

GUIDELINES FOR COMPASSIONATE USE OF LOPINAVIR/RITONAVIR IN SYMPTOMATIC 2019 –COVID -19 PATIENTS

The treatment guidelines are to be implemented for clinical management of Severe Acute Respiratory Infection due to novel Corona virus. Treatment with lopinavir-ritonavir should be restricted to those patients with proven 2019-COVID-19 who present with clinical syndromes of mild pneumonia, severe pneumonia, acute respiratory distress syndrome, sepsis or septic shock (WHO Interim guidance on clinical management of severe acute respiratory infection due to novel corona virus, 28 Jan 2020).

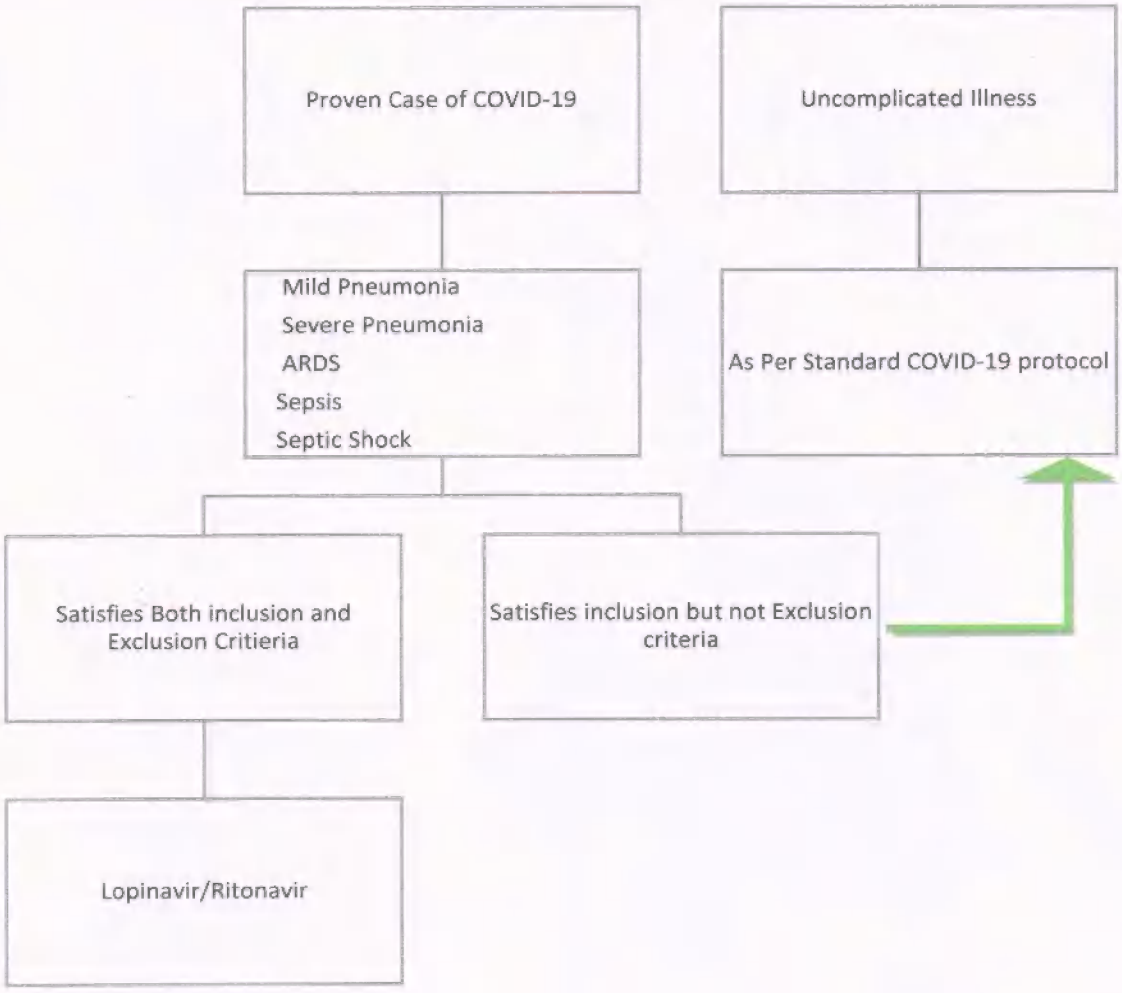
Patient Eligibility criteria:

- Adult over 18yrs of age
- Laboratory confirmation of 2019-COVID-19 infection by RT-PCR from throat swab, sputum or BAL specimen.
- Patients with mild Pneumonia, severe pneumonia, ARDS, Sepsis or septic shock, hospitalized due to symptoms related to nCoV.#
- Informed consent from patient
- Clearance from Medical board constituted for novel corona virus care in the treating Institution or from the Medical College Attached.
- For patients below 18 years of age, clearance from the State Medical Board is required.

Exclusion Criteria:

- Asymptomatic individuals with COVID-19 infection.
- Known allergy or hypersensitivity reaction to Lopinavir / Ritonavir.
- A patient with Hepatic Impairment (ALT over more than five times the normal).
- Use of medications that are contraindicated with Lopinavir / Ritonavir and that cannot be replaced or stopped, It is contraindicated with astemizole, terfenadine, cisapride, ergot derivatives, sildenafil, midazolam , triazolam; lovastatin, simvastatin, pimozide and fluticasone propionate.
- Known HIV infected individual receiving other protease inhibitors containing regimen
- Documented chronic liver disease.

ALGORITHM FOR CASE MANAGEMENT



DOSAGE OF LOPINAVIR / RITONAVIR

ADULTS:

Lopinavir / Ritonavir 200mg/50mg - 2 tablets every 12 hours for 14 days or for 7 days after becoming asymptomatic whichever is earlier

For patients unable to take medicines orally, 400mg Lopinavir / 100 mg Ritonavir 5ml suspension every 12 hours for 14 days or for 7 days after becoming asymptomatic whichever is earlier, via a nasogastric tube.

Administer with caution among persons receiving Rifampicin, Ketoconazole, ethylene estradiol

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LABORATORY INVESTIGATIONS:

- Haemogram
- Liver function test
- Renal function test
- HbA1C and blood sugar, if required
- RT PCR for COVID-19 (respiratory samples, nasopharyngeal samples, oropharyngeal swab, sputum, BAL if available)
- Investigations appropriate for any documented chronic morbidity

LABORATORY SAMPLE COLLECTION-(other than investigations for routine clinical monitoring)

- Blood sample every 48 hours — for PT/INR, LFT, RFT and serum amylase (to monitor drug-induced adverse events)

FREQUENCY AND DURATION OF MONITORING:

Patients should be monitored daily until discharge from the hospital by the Institutional Medical Board.

Patient should be discharged based on the State protocol in concurrence with the opinion of Institutional Medical Board.

Adverse events of Lopinavir –ritonavir

The observed adverse effects with lopinavir/ritonavir are

1. Acute pancreatitis (defined as having)
    a. abdominal pain consistent with acute Pancreatitis
    b. serum amylase at least three times greater than the upper limit of normal)
2. Elevation of ALT to more than five-fold upper limit of normal.
3. Anaphylaxis
4. Bleeding diathesis (INR > 3 without anticoagulant therapy)
5. Diarrhoea.

ROLES AND RESPONSIBILITIES OF TREATING INSTITUTIONS

1. The treating hospital will be responsible for patient management.
2. Prior to initiating treatment with Lopinavir / Ritonavir, the Institutional Medical Board will be responsible for obtaining written Informed Consent in the structured format from the patient or his/her guardian.
3. Patients not consenting to receive Lopinavir / Ritonavir will continue to be monitored and treated as per protocol, with provision of standard of care.
4. The case report forms will have to be filled up by the treating physician and submitted to Institutional Medical board.

ROLES AND RESPONSIBILITIES OF INSTITUTIONAL MEDICAL BOARD

1.Institutional Medical board will decide whether the patient with confirmed novel corona virus infection satisfies the criteria to be initiated on lopinavir-ritonavir.

2.Institutional Medical board will have to assess the patients who have been initiated on lopinavir-ritonavir daily.

3.Institutional medical board will have to ensure that the case report form is filled properly.

4.If patients with high risk contact of confirmed case of nCoV, presents with ARDS or sepsis, the need for initiation of lopinavir-ritonavir should be assessed by Institutional Medical board and should be referred to State Medical Board.

ROLES AND RESPONSIBILITIES OF STATE MEDICAL BOARD

1. If patients with high risk contact of confirmed case of nCoV, presents with ARDS or sepsis, the need for initiation of lopinavir-ritonavir should be assessed by State Medical Board and directive should be given to concerned Institutional Medical Board.

2. Any clarification with regard to compassionate use of lopinavir-ritonavir will be addressed by State Medical Board.

3. Treatment decision regarding use of lopinavir-ritonavir in confirmed nCoV cases in patients less than 18 yrs of age will be addressed by state Medical Board.

#CASE DEFINITIONS OF CLINICAL SYNDROMES

Mild pneumonia	Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty breathing + fast breathing: fast breathing (in breaths/min): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40 and no signs of severe pneumonia.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO2 <90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40. The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome	Onset: new or worsening respiratory symptoms within one week of known clinical insult. Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. Oxygenation (adults):

	• Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH2O, 7 or non-ventilated8) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cmH2O, 7 or non-ventilated8) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cmH2O, 7 or non-ventilated8) • When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non-ventilated patients) Oxygenation (children; OI = Oxygenation Index and OSI = Oxygenation Index using SpO2): • Bilevel NIV or CPAP ≥5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. Children : any hypotension (SBP 2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR 160 bpm in infants and HR 150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

References

1. Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance by WHO Jan 28, 2020.

INFORMED CONSENT FORM FOR COMPASSIONATE USE OF LOPINAVIR-RITONAVIR FOR COVID-19 VIRUS

Institutional Medical board has informed me that I /my relative have been diagnosed with SARS-CoV -2 infection. They have clearly explained to me that there is no effective and approved medication against COVID-19 infection. They have explained to me in detail that there is some scientific evidence regarding the effectiveness of using lopinavir-ritonavir for corona virus infections like SARS in the past. They also explained to me that at present a clinical trial is going on in China to ascertain the efficacy of lopinavir-ritonavir in people affected by COVID-19. They have explained to me that lopinavir-ritonavir has been used in treatment of HIV even in children for more than ten years in India with an acceptable adverse effect profile.

The team of doctors informed me that as I have developed pneumonia due to COVID-19, I might benefit by the restricted Compassionate use of lopinavir-ritonavir. They have clearly explained to me that lopinavir-ritonavir has not been approved for the definitive treatment of COVID-19.They have explained to me in detail that as there are no approved antiviral drugs for COVID-19, and as there is a risk of progression to acute respiratory distress syndrome, lopinavir-ritonavir may be used. They have explained to me about the probable side effects of lopinavir-ritonavir like diarrhea, hypersensitivity, pancreatitis, gastritis and hepatitis. They have made it clear that the standard treatment for COVID-19 infection will be continued irrespective of my decision regarding the compassionate use of lopinavir-ritonavir. Knowing that lopinavir-ritonavir is not an approved medication for the treatment of novel corona virus infection, I fully agree to the restricted public health emergency use of this drug for the treatment of my novel corona virus infection.

Name

Relation

Signature

Institutional Medical Board Members

Name

Signature

The advisory may be followed up by the treating team and the Hospital Medical Board.

If there is any doubt, teams may consult the State Medical Board.

Principal Secretary